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amended

mutagenizing nucleic acid encoding a first polypeptide [of interest], and
expressing the mutagenized nucleic acid to produce the collection of mutant
polypeptides.

48. (amended) The method of claim 46 wherein identification of mutant polypeptides
that exhibit less of, or have less potential to exhibit, an allergic response is accomplished by
exposing the mutant polypeptides to individual IgE antibodies or antibody fragments that are
reactive to the first polypeptide [of interest].

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51. (amended) The method of claim 46 wherein the [desired] advantageous
characteristic is T cell activation.

52. (amended) The method of claim 46 wherein the [desired] advantageous
characteristic is an immune characteristic involved in allergic desensitization.

53. (amended) The method of claim 46 wherein identification of mutant polypeptides
that exhibit less of, or have less potential to exhibit, an allergic response is carried out prior to,
simultaneous with, or following identification of mutant polypeptides that retain the [desired]
advantageous characteristic.

Please cancel claims 54-88.

Remarks

Amendments to the Claims

Claims 1, 20 and 46 have been amended to incorporate the limitations of claim 4. Claim
4 has been cancelled. Claim 1 has also been amended to clarify that there are two steps:

screening for altered binding and screening for retention of a desirable activity.

Restriction Requirement

Applicants greatly appreciate the rejoinder of claims 46-53 with claims 1-28. Claims 29-45 and 54-88 have been cancelled.

Rejections under 35 U.S.C. 112

Claims 1-17, 19-23, and 46-53 were rejected under 35 U.S.C. 112, as indefinite. These rejections are respectfully traversed if applied to the amended claims.

The claims have been amended to delete reference to "desired" and "of interest" and to correct antecedent basis. Claim 1 has been amended to more clearly recite that it is a method of obtaining claim. Claims 22-23 have been amended to a method of use claim, and claim 22 has been rewritten in independent form.

Rejections under 35 U.S.C. 102 and 103

Claims 1-6, 8, 9, 11-14, 16, 17, 19, 21, 46-49, 52, and 53 were rejected under 35 U.S.C. 102(a) as disclosed by Hakkaart, et al., Allergy 51, 165-172 (1998). Claims 1-6, 8, 9, 11-14, 16, 17, 19, 21-23, 46-49 and 52-53 were rejected under 102 as disclosed by Smith, et al. J. Aller. Clin. Immunol. 101:423-425 (1998). Claims 1-3 and 6 were rejected under 102 as disclosed by Jespers, et al., J. Mol. Biol. 269(5):704-718 (1997). Claims 6, 7 and 50 were rejected under 35 U.S.C. 103 as obvious over Hakkaart et al., in view of Steinberger, et al., J.B.C. 271:10967-10982 (1996). Claim 20 was rejected under 35 U.S.C. 103 as obvious over Hakkaart et al., in combination with Espanion, DTW 103(8-9):320-8 (1996). These rejections are respectfully

traversed if applied to the amended claims.

Hakkaart

change to 100/23

Hakkaart discloses epitope mapping of a dust mite allergen, then semi-selective modification of individual amino acid residues so that the importance of the individual residues to IgE binding could be determined. The mutant proteins were screened for binding to monoclonal antibodies (Page 168, col. 2) to examine the effect of the mutation on binding of IgE to the protein. Histamine release is a function of IgE binding - it is a very undesirable property, being largely responsible for the redness and itchiness associated with allergies. Although it was observed that the polypeptides still bound IgE and therefore released histamine, there was no screening for an "advantageous" property, such as inducing IgG production, which could be used to induce tolerance in an allergic patient.

Smith

not concentrate
in 5 cups with ac
just claim 1. Also, claim of mutation
retaining
to IgE
not only
to IgG

Smith describes site-directed mutation of a dust mite allergen that alters its three dimensional structure. The mutated antigens were screened for binding to monoclonal antibody and to IgE. The mutants were also screened to see if the *in vivo* reaction was altered by the mutation. The results demonstrated that an undesirable characteristic (binding to IgE) was decreased by mutation, but there was no screening for an advantageous characteristic (such as elicitation of IgG to induce tolerance).

use other of g. mite

Jespers

Jespers is similar to Hakkaart et al., and Smith, et al., except that the protein is not an

change to 100/23
pages HS 105
not need
cell. per

Hakkart is discussed above. Steinberger describes the construction of a combinatorial

Hakkaart is discussed above. Espanion is a review of the production of transgenic animals. Since Hakkaart fails to disclose or make obvious the claimed method generally, the combination of Hakkaart with Espanion fails to make obvious the method using transgenic

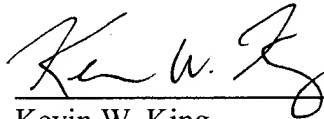
U.S.S.N. 09/247,406
Filed: February 10, 1999
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animals.

In summary, none of the cited art discloses two steps, using a protein associated with an unfavorable immune response, where the protein is mutated, screened for binding to a monospecific antibody, then screened for retention of a favorable property, such as the ability to induce production of IgG or retention of binding of T cells so that one could then use the mutated proteins to more safely induce tolerance.

Allowance of claims 1-3, 5-17, 19-23, and 46-53, as amended, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an Appendix to facilitate review by the Examiner.

Respectfully submitted,



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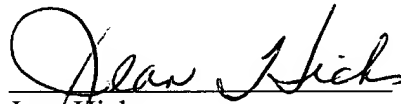
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U.S.S.N. 09/247,406
Filed: February 10, 1999
AMENDMENT

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with sufficient first class postage in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231 on the date shown below.

Date: November 27, 2000


Jean Hicks

Appendix: Claims as pending upon entry of this amendment

1. (amended) A method to identify mutant polypeptides having altered antibody reactivity as compared to a first polypeptide, while retaining at least one desirable characteristic of the first polypeptide comprising

providing a collection of mutant polypeptides wherein the amino acid sequence of each mutant polypeptide differs in at least one position from [a] the first polypeptide [of interest], and identifying those mutant polypeptides within the collection that (1) have an alteration in antibody reactivity compared to the first polypeptide [of interest], wherein either or both the antibody reactivity and the alteration in the antibody reactivity are associated with an undesirable immune response, and (2) retain at least one [desired] advantageous characteristic of the first polypeptide.

wherein alteration in the antibody reactivity is determined by exposing the mutant polypeptides to [individual] antibodies or antibody fragments that are monospecific for the first polypeptide [of interest] and then screening for retention of the advantageous characteristic.

2. (amended) The method of claim 1 wherein the collection of mutant polypeptides is provided by mutagenizing nucleic acid encoding [a] the first polypeptide [of interest], and expressing the mutagenized nucleic acid to produce the collection of mutant polypeptides.

3. (amended) The method of claim 2 wherein the nucleic acid encoding the first polypeptide [of interest] is mutagenized such that a collection of randomly mutagenized nucleic acids is produced which encodes a collection of randomly mutant polypeptides.

Please cancel claim 4.

5. (amended) The method of claim [2] 1 wherein the antibody reactivity is the undesirable immune response, wherein the undesirable immune response is mediated by the antibody reactivity, [wherein the antibody reactivity is involved in the undesirable immune response, wherein the antibody reactivity is associated with the undesirable immune response,] or a combination of these.

6. The method of claim 1 wherein the antibodies or antibody fragments that are monospecific for the polypeptide are either monoclonal antibodies derived from mammals or antibodies or antibody fragments derived from a combinatorial library.

7. The method of claim 6 wherein the antibodies or antibody fragments are antibody fragments derived from a combinatorial library.

8. The method of claim 1 wherein the antibody reactivity is reactivity to IgA antibodies, reactivity to IgD antibodies, reactivity to IgE antibodies, reactivity to IgG antibodies, or reactivity to IgM antibodies.

9. (amended) The method of claim 8 wherein the antibody reactivity is reactivity to IgE antibodies that are reactive to the first polypeptide [of interest].

10. (amended) The method of claim 9 wherein the [desired] advantageous characteristic

is T cell activation.

11. (amended) The method of claim 9 wherein the [desired] advantageous characteristic is an immune characteristic involved in desensitization.

12. (amended) The method of claim 1 wherein identification of mutant polypeptides that have an alteration in antibody reactivity is carried out prior to, simultaneous with, or following identification of mutant polypeptides that retain the [desired] advantageous characteristic.

13. (amended) The method of claim 1 wherein the [desired] advantageous characteristic is a bioactivity present in the first polypeptide [of interest].

14. The method of claim 13 wherein the bioactivity is selected from the group consisting of enzymatic activity, receptor binding, anticancer activity, immunosuppressive activity, immunostimulatory activity, immune characteristic, alteration of the function of immune system cells, antibiotic activity, antiviral activity, and trophic activity.

15. The method of claim 14 wherein the bioactivity is T cell activation or B cell activation.

16. The method of claim 14 wherein the bioactivity is an immune characteristic involved in desensitization.

17. The method of claim 14 wherein the bioactivity is an alteration of the function of immune system cells, wherein the cells are dendritic cells, macrophages, mast cells, basophils, or eosinophils.

Please cancel claim 18.

19. The method of claim 1 further comprising identifying the mutations present in the identified mutant polypeptides, and combining two or more of the identified mutations in a single mutant polypeptide.

20. The method of claim 1 further comprising expressing the polypeptide in a transgenic animal or plant.

21. The method of claim 20 wherein the polypeptide of interest naturally occurs in non-transgenic animals or plants of the same type as the transgenic animal or plant. *no mutation, first paper*

22. (amended) [The] A method of [claim 1 further] altering an antibody mediated or associated reaction in an individual comprising

administering one or more times to an individual one or more polypeptides [each derived from at least one of the identified mutant polypeptides] having altered antibody reactivity while retaining desirable characteristics identified by a process wherein a collection of mutant polypeptides is provided, wherein the amino acid sequence of each mutant polypeptide differs in at least one position from a first polypeptide having at least one advantageous characteristic, and

identifying those mutant polypeptides within the collection that (1) have an alteration in antibody reactivity compared to the polypeptide of interest, wherein either or both the antibody reactivity and the alteration in the antibody reactivity are associated with an undesirable immune response, and (2) retain at least one advantageous characteristic,

wherein alteration in the antibody reactivity is determined by exposing the mutant polypeptides to antibodies or antibody fragments that are monospecific for the first polypeptide.

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21. (amended) The method of claim 20 wherein the first polypeptide [of interest] naturally occurs in non-transgenic animals or plants of the same type as the transgenic animal or plant. Please cancel claims 24-45.

46. (amended) A method comprising
providing a collection of mutant polypeptides wherein the amino acid sequence of each mutant polypeptide differs in at least one position from a first polypeptide [of interest], wherein the polypeptide [of interest] is an allergen, and
identifying those mutant polypeptides within the collection that (1) exhibit less of, or have less potential to exhibit, an allergic response than the polypeptide of interest, wherein either or both the antibody reactivity and the alteration in the antibody reactivity are associated with an undesirable immune response, and (2) retain at least one desired characteristic.

47. (amended) The method of claim 46 wherein the collection of mutant polypeptides is provided by
mutagenizing nucleic acid encoding a first polypeptide [of interest], and
expressing the mutagenized nucleic acid to produce the collection of mutant polypeptides.

48. (amended) The method of claim 46 wherein identification of mutant polypeptides that exhibit less of, or have less potential to exhibit, an allergic response is accomplished by exposing the mutant polypeptides to individual IgE antibodies or antibody fragments that are reactive to the first polypeptide [of interest].

49. The method of claim 48 wherein the IgE antibodies or antibody fragments that are reactive to the polypeptide of interest are either monoclonal IgE antibodies derived from mammals or IgE antibodies or antibody fragments derived from a combinatorial IgE library.

50. The method of claim 49 wherein the IgE antibodies or antibody fragments are IgE antibody fragments derived from a combinatorial IgE library.

51. (amended) The method of claim 46 wherein the [desired] advantageous characteristic is T cell activation.

52. (amended) The method of claim 46 wherein the [desired] advantageous characteristic is an immune characteristic involved in allergic desensitization.

53. (amended) The method of claim 46 wherein identification of mutant polypeptides that exhibit less of, or have less potential to exhibit, an allergic response is carried out prior to, simultaneous with, or following identification of mutant polypeptides that retain the [desired] advantageous characteristic.

Please cancel claims 54-88.